REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-4, 10-15, 26 and 120-127 are in this case. Claims 12-15 and 125 have been rejected under 35 U.S.C. 112, second paragraph. Claims 1-4, 10-15, 120-127 have been rejected under 35 U.S.C. 103(a). Claims 2, 12 and 125 have now been amended. New claims 128-130 have now been added.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 12-15 and 125 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states that an enzyme selected incapable of converting modified glutamate into glutamate is confusing for the reason that one would not need an enzyme to convert glutamate to glutamate and further lacks antecedent basis.

The Examiner's rejection is respectfully traversed. Claims 12 and 125 have now been amended.

Applicant wishes to point out that the claimed enzyme is incapable of converting modified glutamate to glutamate. This is substantially different from converting glutamate to glutamate, which is not claimed and indeed does not make sense. Applicant wishes to clarify that the modified glutamate refers to a substance which results from glutamate metabolism by the glutamate modifying enzyme i.e., a glutamate metabolite. Such a glutamate metabolite can be converted to glutamate by a glutamate modifying enzyme. In order to avoid this reversible reaction the enzyme is selected incapable of mediating this reverse reaction.

A detailed description of glutamate modifying enzymes and glutamate metabolites is provided throughout the application. See for example in page 3 lines 18-23.

Notwithstanding the above and in order to expedite prosecution in this case, Applicant has elected to replace the phrase "modified glutamate" in claims 12 and

125 to a "glutamate metabolite" for cosmetic reasons. Support for this can be found in page 3 line 20 of the application.

In view of the above arguments and amendments Applicant believes to have overcome the rejections under 35 U.S.C 112 second paragraph. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Matthews et al. in view of Geng et al. or

http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm and

http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html

The Examiner has rejected claims 1-4, 10-15 and 120-127 under 35 U.S.C. 103(a) Matthews et al. (J. Neurochemistry, v75, 2000) in view of Geng et al. (J. Neurochemistry vol. 68 no. 6 1997) or http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm and http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html.

Specifically, the Examiner states that one of ordinary skill in the art would have been motivated to have administered a glutamate modifying enzyme such as GOT (http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm) along with its respective co-substrates (http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html, Geng et al.) to a subject in need thereof with a reasonable expectation for successfully decreasing extracellular glutamate levels because Matthews teach GPT to be useful in decreasing glutamate levels and useful in protecting against glutamate neurotoxicity.

The Examiner's rejection is respectfully traversed.

The claimed invention relates to the novel discovery showing that extracellular brain glutamate may be reduced by enhancing the brain to blood glutamate efflux without the need for administering the drug directly to the brain or formulate it such that it passes the BBB.

Specifically, according to the claimed invention, extracellular brain glutamate can be reduced by the systemic administration of a glutamate modifying enzyme to

the peripheral blood of the subject (e.g., i.v.) thereby enhancing the brain to blood glutamate efflux.

Matthews et al. understood the importance of reducing extracellular brain glutamate but in the absence of any possibility to target the enzyme to the brain they had to work with in vitro cultures of mouse cortices.

In fact Matthews et al. teach away from *in vivo* use of glutamate modifying enzymes for treating glutamate related neurotoxicity as can be learnt from the following recitations:

Page 1050 right column, line 29:

> *"In the treated setting, little glutamate would be available to contribute to the total medium glutamate pool, ...".*

And further in line 34:

> *"The other major limitation to using glutamate-degrading enzymes as neuroprotectants is their large molecular size. "Techniques to disrupt the blood-brain barrier, enhance blood-brain barrier transcytosis, or bypass the blood-brain barrier through retrograde axonal transport will be needed before this strategy can be evaluated in vivo."*

Thus, not only does Matthews et al. indicate that the amount of glutamate that will be available for enzymatic metabolism will be limited (resulting in inefficiency of the treatment), but that the large molecular size of the enzyme is clearly precluded from crossing the BBB. Thus, Matthews et al. teach away from direct administration of the enzyme to the brain as well as it's systemic administration through the peripheral circulation.

In view of the foregoing it is clear that in sharp contrast to Examiner's assertion Matthews et al. could not have motivated the skilled artisan to administer glutamate modifying enzymes to a subject in need thereof with a reasonable degree of success to protect against glutamate neurotoxicity.

Like Matthews et al., Geng et al. teach away from the claimed invention in presenting obstacles associated with using in vivo models i.e., penetration through the BBB *("It is difficult to study hypoglycemia-induced neuronal injury in vivo..."* Page 2501, right column, first paragraph).

Thus, it is Applicant strong opinion that the present invention as now claimed is novel and non-obvious over Matthews et al. either alone or in combination with Geng et al., http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm or http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html. Applicant therefore requests withdrawal of the rejection.

Claim Rejections – 35 U.S.C. § 103

WO 99/21565 in view of Matthews et al. and

http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm and

http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html.

The Examiner has rejected claims 1-4, 10-15, 26, 120-125 under 35 U.S.C. 103(1) as being unpatentable over WO 99/21565 in view of Matthews et al. (supra) and ***http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html.***

Specifically, the Examiner states that one of ordinary skill in the art would have been motivated to have administered a glutamate modifying enzyme such as GOT (http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm) along with its respective co-substrates (http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html) to a subject in need thereof with a reasonable expectation for successfully decreasing extracellular glutamate levels because Matthews teach GPT to be useful in decreasing glutamate levels and useful in protecting against glutamate neurotoxicity; and that reducing blood glutamate levels is intrinsic to the administration of GOT substrate as taught by WO 99/21565. The Examiner's rejections are respectfully traversed.

Applicant wishes to point out that the art of WO 99/21565 suggests the treatment of metabolic disorders associated with impaired mitochondrial function by administration of a Kreb's cycle intermediate which is a substrate of a glutamate

modifying enzyme. WO 99/21565 is silent with respect to the administration of glutamate modifying enzymes for the treatment of medical conditions of the CNS. Applicant is puzzled by Examiner's statement that reducing blood glutamate levels is intrinsic to the administration of GOT substrate as taught by WO 99/21565. **An effect is intrinsic to a particular composition administered.** However, the composition administered to the subject in the case of WO 99/21565 is profoundly different than that taught by the claimed invention (**enzyme vs. substrate**).

As described in length hereinabove, Matthews teaches away from administering glutamate modifying enzymes for reducing extracellular brain glutamate, in stating that the enzyme is too large to cross the BBB and inefficient to eliminate the extracellular brain glutamate.

Thus, Applicant fails to understand how the art of WO 99/21565 (teaching administration of substrates and not enzymes) together with Matthews et al. (teaching away from enzyme administration) can be combined to arrive at the present invention as claimed.

Thus, it is Applicant strong opinion that the present invention as now claimed is novel and non-obvious over WO 99/21565, Matthews et al. either alone or in combination with http://www.bio.mtu.edu/campbell/bl4820/lectures/lec4/gotw41.htm or http://www.chem.qmul.ac.uk/iubmb/enzymeEC2/0601a/html. Applicant therefore requests withdrawal of the rejection.

In view of the above amendments and remarks it is respectfully submitted that claims 1-4, 10-15, 26 and 120-130are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Martin D. Moynihan,
Registration No. 40,338

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